PATHOLOGY TEAM
439

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Thromboembolism

Objectives:

- Understand the basic pathology of thrombogenesis and the risk factors for development of deep vein thrombosis.

- Know the types of embolus than can occur and the pathology of pulmonary embolism.

Index:
Important
NOTES
Extra Information

Thrombosis

- It is a process by which a **thrombus is formed**. It represents hemostasis in the intact vascular system.
- It is **intravascular coagulation** of blood and it often causes significant interruption to blood flow.

Thrombus

It is a **solid mass** (blood clot) made up of blood constituents which **develops in artery or vein**.

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Components of the hemostatic process

Endothelial cells

(should be intact to protect against thrombosis)
are resistant to the thrombogenic influence of platelets and coagulation proteins. Intact endothelial cells are thromboresistant.

Platelets

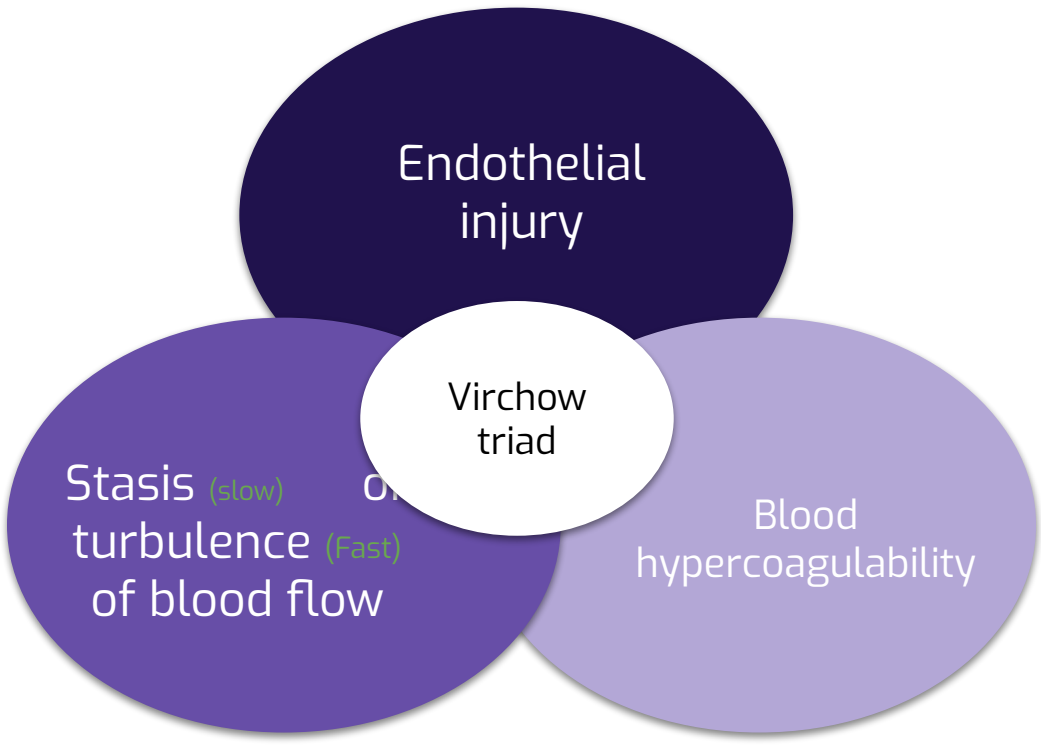
maintain the integrity of the vascular endothelium and participate in endothelial repair. **They form platelet plugs and promote the coagulation cascade.**

Coagulation Cascade

is a major contributor to thrombosis. It is a series of enzymatic conversions, that end in the formation of thrombin. Thrombin then converts the soluble plasma protein fibrinogen into **the insoluble protein fibrin.** And fibrin is a **constituent of the thrombus.**

PATHOGENESIS

Three primary influences called as Virchow triad predispose to thrombus formation:



It results from interaction of platelets, damaged endothelial cells and the coagulation cascade. All 3 are component of the hemostatic process.

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Fibrinolysis
(thrombus dissolution)

Activation of the clotting cascade induces coagulation. It also **triggers the fibrinolytic cascade** that **limits the size** of the final clot. It runs concurrently with thrombogenesis.

Fibrinolytic cascade helps **dissolve the thrombus** and therefore restores blood flow in vessels occluded by the thrombus.

In the fibrinolytic cascade:
The thrombus is dissolved by plasmin.

Endothelial cells

- The endothelium is a single cell thick lining of endothelial cells and it is the inner lining of the entire cardiovascular system (arteries, veins and capillaries) and the lymphatic system.
- It is in direct contact with the blood/lymph and the cells circulating in it.
- Endothelial structural and functional integrity is fundamental to the maintenance of vessel wall homeostasis and normal circulatory function.

Endothelial injury
A major cause of thrombosis in the heart or arteries

The following **conditions** lead to **chronic subtle endothelial dysfunction/injury**:

- **Hypertension**
- Scarred valves
- Bacterial endotoxins
- **Radiation**
- **Hypercholesterolemia**
- **Cigarette smoking**

Endothelial injury leads to:

Exposure of subendothelial ECM i.e the basement membrane

Adhesion of platelets

Release of tissue factor and ultimately thrombosis

Endothelial injury can **contribute to thrombosis** in several clinical settings e.g:

- Endocardial injury due to **myocardial infarction**.
- **Ulcerated plaques in atherosclerotic arteries.**
- Traumatic or inflammatory vascular injury

The "abnormal blood flow" part is in Girl's slides only

Abnormal blood flow

disruption of laminar blood flow can bring platelets into contact with the endothelial cell activation

Stasis (slow)
plays a major role in the development of **venous thrombi**

OR

Turbulence (fast)
contributes to **arterial** & bifurcation of arteries and **cardiac chambers** thrombosis by causing endothelial injury or dysfunction

Abnormal blood flow **contributes for thrombosis** in several clinical settings:

- Ulcerated atherosclerotic plaques.
- Abnormal aortic and arterial dilations.
- Acute myocardial infarction.
- Mitral valve stenosis.
- Hyperviscosity syndromes.
- Sickle cell anemia.

Hypercoagulability

Definition	Any change of the coagulation pathways that predisposes to thrombosis.	
Can be divided into:		
Primary (inherited) hypercoagulable states	Secondary (acquired) hypercoagulable states. they can be high risk or low risk	
	High risk	Lower risk
- e.g. mutation in factor V gene or prothrombin gene. - Anti-thrombin III deficiency. - Protein C or S deficiencies. - Fibrinolysis defects.	**- Prolonged bed rest or immobilization** - **Myocardial infarction** (due to endothelial injury), Atrial fibrillation **- Tissue damage (surgery, fracture, burns)** - **Cancer** (Release of procoagulant tumor products) **- Prosthetic cardiac valves** **- Disseminated intravascular coagulation** (coagulation happens in very strong way, Thrombin generation) - Heparin-induced thrombocytopenia - Antiphospholipid antibody syndrome (lupus anticoagulant syndrome)	- (Cardiac problem) Cardiomyopathy. **- Nephrotic syndrome.** **- Hyperestrogenic states (pregnancy).** **- Oral contraceptive use.** - Sickle cell anemia. **- Smoking.** **- Renal problem.**

Thrombotic disorders

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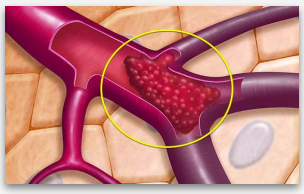
<table>
<tr><td>Definition
  </td><td colspan="2">- Lots of thrombus develop in different parts of the body

- Congenital and acquired diseases characterized by formation of thrombus that obstructs vascular blood flow locally or detaches and embolizes to occlude blood flow downstream (thromboembolism).</td></tr>
<tr><td>Types</td><td colspan="2">Anti-thrombotic (hemorrhagic), Pro-thrombotic, Disseminated intravascular coagulation</td></tr>
<tr><td>Anti-thrombotic (hemorrhagic)</td><td colspan="2">leading to pathologic bleeding states such as:

hemophilia, Christmas disease and von Willebrand disease.</td></tr>
<tr><td rowspan="3">Pro-thrombotic</td><td colspan="2">leading to hypercoagulability with pathologic thrombosis:</td></tr>
<tr><td>Hereditary thrombophilia</td><td>• Is a prothrombotic familial syndrome.
• Characterized by recurrent venous thrombosis and thromboembolism.
• Can be caused by deficiency of antithrombotic proteins e,g. antithrombin 3, protein C, and protein S.
• Factor V Leiden thrombophilia is a genetically inherited prothrombotic disorder of blood. Factor V Leiden is a mutated form of human factor V that causes an increase in blood clotting (hypercoagulability).</td></tr>
<tr><td>Anti-phospholipid antibody syndrome</td><td>•
• Is a prothrombotic hypercoagulable autoimmune multisystem disorder caused by the presence of antiphospholipid antibodies.
• Is characterized by recurrent thrombosis and embolism and fetal loss in pregnancy.
• Patients have prolonged partial thromboplastin time (PTT).
• It is sometimes associated Systemic Lupus Erythematosus (systemic autoimmune disease see in women in reproductive age group) and so this antibody is also known as lupus anticoagulant.</td></tr>
<tr><td>Disseminated intravascular coagulation</td><td colspan="2">Is both prothrombotic and antithrombotic disorder are happening at the same time characterized by widespread thrombosis and hemorrhage resulting from the consumption of platelets and coagulation factors.</td></tr>
</table>

Thrombus morphology

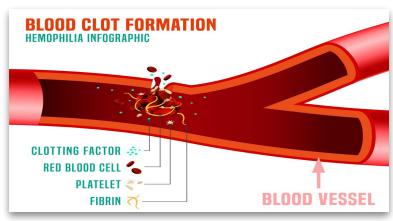
1. Thrombi may develop **anywhere in the cardiovascular system**, the cardiac chambers valve cusps, arteries, veins, or capillaries. **They vary in size and shape, depending on the site of origin.**

2. **Arterial or cardiac** thrombi usually **begin at a site of endothelial injury** (e.g., atherosclerotic plaque) or **turbulence** (vessel bifurcation). **Venous** thrombi characteristically occur in sites of **stasis**.

3. **Arterial** thrombi grow in a **retrograde direction** from the point of attachment (i.e. toward the heart). **Venous** thrombi extend **in the direction** of blood flow (i.e. toward the heart).

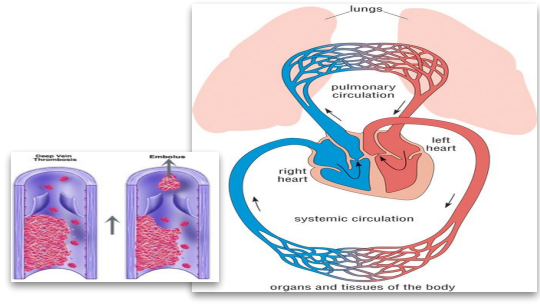
4. The propagating tail of either thrombi may not be **well attached** (particularly in veins) is **prone to fragmentation**, **creating an embolus.**

Component of thrombus
made up of fibrin, platelets and red blood cell and few inflammatory cells.



Mural thrombus

Definition	When arterial thrombi arise in heart chambers or in large blood vessels such as the aortic lumen
Cause	Abnormal myocardial contraction or endomyocardial injury promotes cardiac mural thrombi.
Characterized by	**Lines of Zahn** Big thrombi formed in the heart or aorta may have apparent laminations, called lines of Zahn seen grossly (and microscopically). Lines of Zahn are produced by alternating **pale layers** of platelets admixed with **some fibrin** and **darker layers** containing **more red cells.**



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Thrombi are significant because:

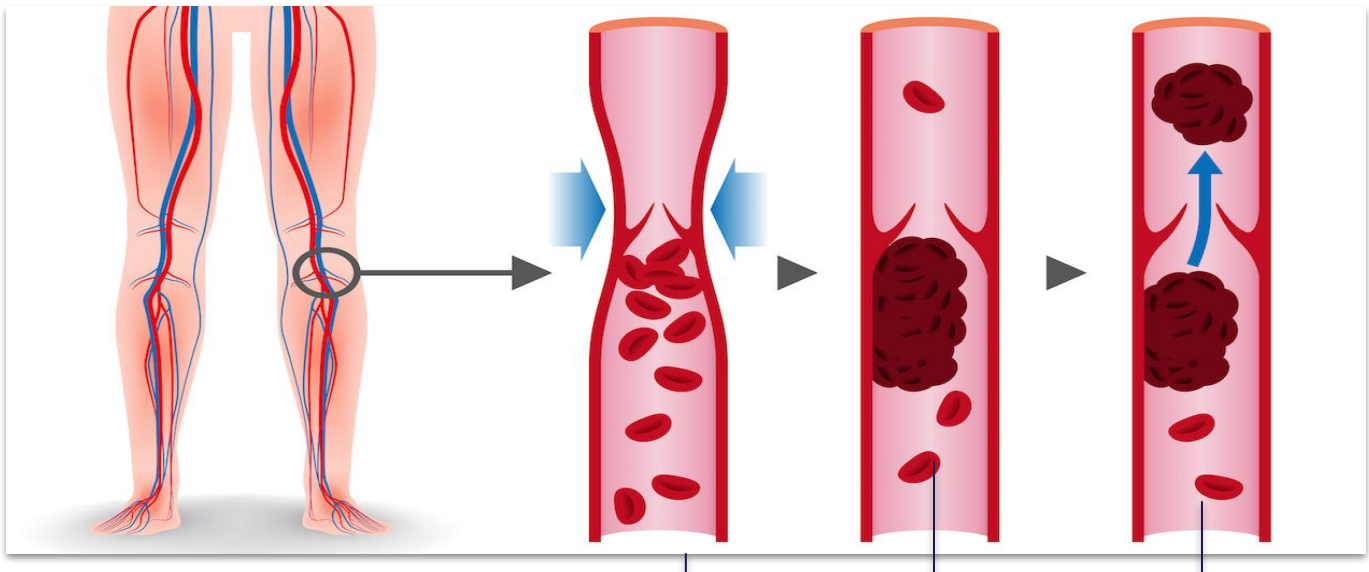
1. They cause **obstruction** of arteries and veins lead to ischemia then necrosis & infraction

2. They are potential sources of **emboli** (Travel to distant site and block blood vessel)

Clinical Features

Clinical effects **depend on the site of thrombosis**:

Venous thrombi	Arterial thrombi
have capacity to embolize to the lungs (By pulmonary artery) and can cause death.	can cause vascular obstruction at critical sites in the systemic circulation and cause serious consequence e.g. **ischemia and necrosis.**



Normal regular blood vessel (Vein) with blood going through it

Thrombus formed in the wall of BV, it's solid mass made of RBCs, Fibrin, platelets and inflammatory cells

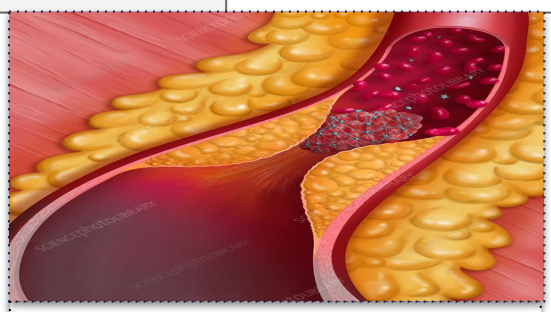
Then grow slow and become friable, specially when blood flow hits against this thrombus leads to detach some pieces, each pieces called embolus that will travel through blood stream and block small blood vessel & cause hypoxia - The process called embolization.

Types of Thrombus

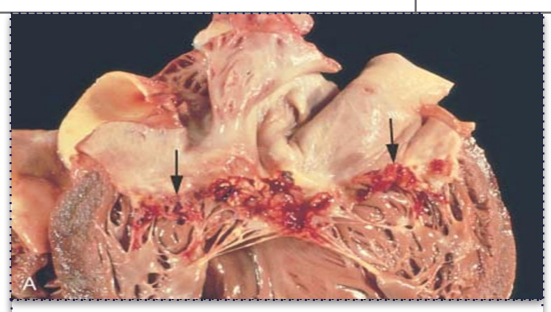
	A. Arterial thrombi	B. Venous thrombi Also called phlebothrombosis
Nature	Usually occlusive	Is almost invariably occlusive, and often takes the **shape of the vein**.
Location	It's usually superimposed on an **atherosclerotic plaque** and are firmly adherent to the injured arterial wall (Mural) usually begin at a **site of endothelial injury** (e.g., atherosclerotic plaque) or **turbulence** (vessel bifurcation)	Because these thrombi form in a relatively static environment, they contain more enmeshed erythrocytes and are therefore known as **red**, or **stasis thrombi.**
Direction	Grow in a **retrograde direction** from the point of attachment (i.e. toward the heart) Grow toward the heart which make it opposite to the blood flow	**Extend in the direction** of blood flow (i.e. toward the heart). Grow toward the heart which make it along the blood flow
Most common affected sites	In descending order, are 1. **coronary** (develop MI) 2. **cerebral** (develop CV stroke), 3. **femoral** arteries (develop gangrene in the limbs)	The veins of the **lower extremities** (90% of cases).
Gross appearance	**Gray-white and friable**	Red and hemorrhagic

C. Thrombi on the heart valves

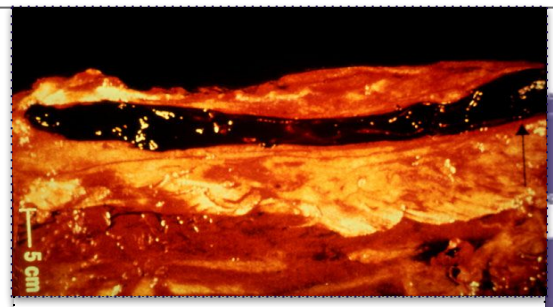
Defension	Thrombi on Heart Valves are called as **vegetations**. They can be infective or sterile	
Types	**Infective vegetations**	**Sterile vegetations**
	Microorganism such as bacterial or fungal blood-borne infections may result in the development of large thrombotic masses on heart valves.	**-Nonbacterial thrombotic endocarditis (marantic):** is non-infective vegetations on valves in patients with - **hypercoagulable states** - **subtle endothelial abnormalities** - **malignancy and other chronic debilitating diseases.** -Patients with **systemic lupus erythematosus** can have noninfective, **verrucous (Libman-Sacks) endocarditis**. (less common)



Arterial thrombi



Vegetation



Venous thrombi

Deep vein thrombosis (DVT) & Thrombophlebitis

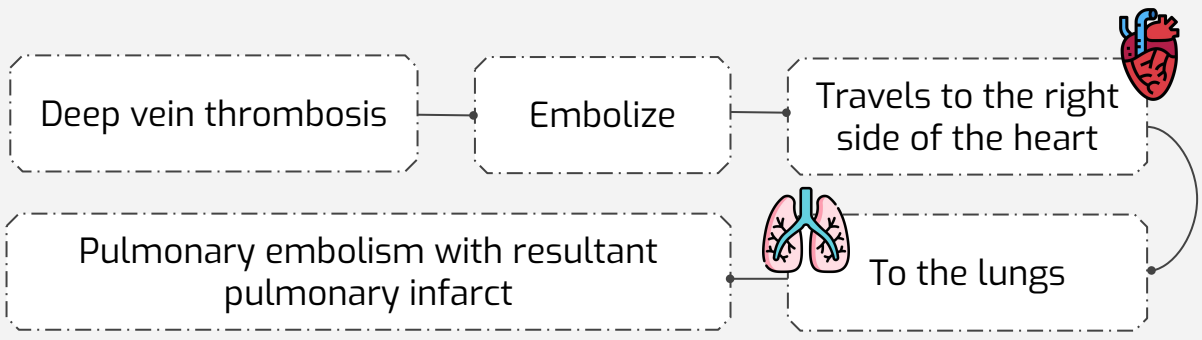
Definition

Deep vein thrombosis is a venous thrombosis that arises in the deep veins of the legs. They occur with stasis (someone being immobilized for long time) or in hypercoagulable states.

Often associated **with inflammation** and then it is termed **thrombophlebitis**

Complications

DVT may **embolize to the lungs** giving rise to **pulmonary embolism** with resultant pulmonary infarct.



Clinical features

DVTs are **asymptomatic** (with local pain & edema) in approximately 50% of affected individuals and are recognized only in retrospect after embolization

Site

Common in deep the larger leg veins at or above the knee (e.g. popliteal, femoral, and iliac veins)

Common **predisposing factors** for DVT

(same as factors predisposing to hypercoagulable state)

- **Bed rest and immobilization**
- **Trauma, surgery, and burns**
- Heart problem such as Congestive heart failure (a cause of impaired venous return)
- **Tumors**
- **Advanced age**
- **Pregnancy**:
  - The potential for amniotic fluid infusion into the circulation at the time of delivery can cause thrombogenesis
  - Late pregnancy and the postpartum (after delivery) period are also associated with systemic hypercoagulability

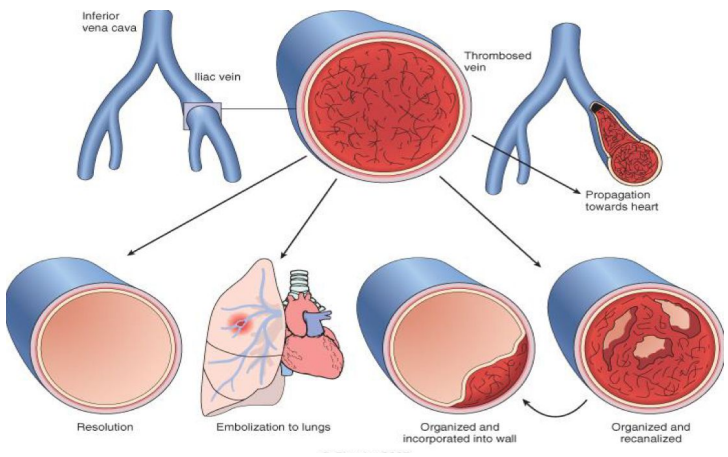
Postmortem clots

At autopsy, postmortem (after death) clots may be confused for venous thrombi.

Postmortem clots	Red (venous) thrombi
Rubbery and Gelatinous	Firmer
They have a **dark red dependent portion** where red cells have settled by gravity and **a top layer of yellow** fat supernatant resembling melted and clotted chicken fat.	On cut section reveal vague strands of pale gray fibrin. Rich admixture of RBCs and appear red
They are **not attached** to the underlying wall	Almost always **have a point of attachment**

Fate of thrombi

- Resolution
- Propagation (start growing)
- Embolism (blocage)
- Organization to the side and recanalization (New channels form to allow BF)
- Organization and incorporation into the wall (become part of the wall)



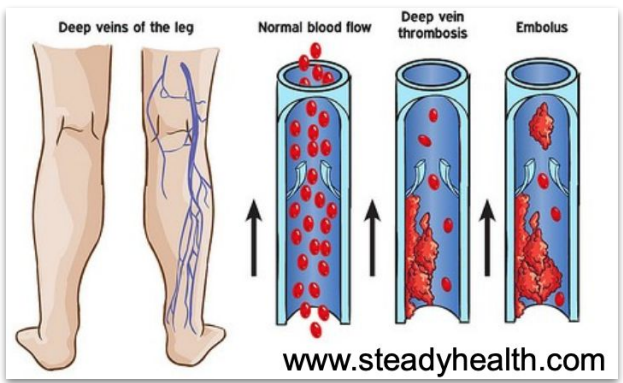
Embolism

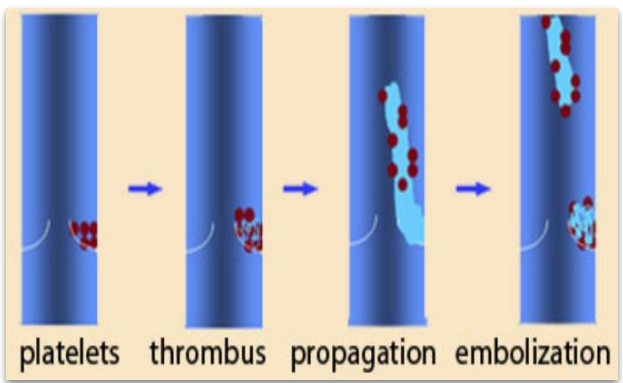
Embolus (plural: emboli) : a **Detached** intravascular (inside BV) solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin.

majority of the emboli represent some part of a dislodged thrombus, hence the commonly used term thromboembolism.

The emboli ultimately lodge in vessels too small to permit further passage, resulting in partial or complete vascular occlusion leading to ischemic necrosis of distal tissue, (infarction).

Depending on the site of origin, emboli may lodge in the pulmonary or systemic circulations. embolus will travel to a distant vessel, where it will block & will cause hypoxia and ischemic injury leading to infarction





Types of Embolism

Pulmonary embolism

In more than 95% of cases, venous emboli originate from deep leg vein thrombi above the level of the knee

Site of lodging & occlusion	Pulmonary vasculature. 1. Depending on the size: occlude main pulmonary artery, or impact across the bifurcation (**saddle embolus,** because the the bifurcation looks like a saddle) or pass out into the smaller, branching arterioles of the pulmonary circulation. 2. **paradoxical embolism:** embolus may pass through interatrial or interventricular defect to gain access to the systemic circulation by going through the septum to the left side of the heart
Complications	- Most (60-80%) are clinically silent because they are small. - when **more than 60%** of the pulmonary circulation is **obstructed** by emboli. Sudden death, infarction, right heart failure (cor pulmonale) occurs.

Systemic thromboembolism (arterial emboli)

Site of lodging & occlusion	- Arteriolar circulation. - Major sites are the lower extremities (75%) and the brain (10%) Most arise from the **intracardiac mural thrombi (80%)** valves & chambers if left side of heart
Complications Girl's slides only	consequences depend on the extent (and size) of collateral vascular supply in the affected tissue, the tissue's vulnerability to ischemia, and the caliber of the vessel occluded. • Causes infarction of tissues supplied by the artery

Fat embolism

Site of lodging & occlusion	• Microscopic fat globules may be found in the circulation after fractures of **long bones** (which have fatty marrow) or subcutaneous tissue or abdomen or , rarely, in **soft tissue trauma and burns** (because fat start burning lead to blood vessel rupture). • Fat is released by bone **marrow** or **adipose tissue injury** and enters the circulation through rupture of the blood vessels and act as an embolus.
Complications	• Less than 10% of patients have any clinical findings. • But when they have symptoms → Fat embolism syndrome is characterized by pulmonary insufficiency, neurologic symptoms, anemia, and thrombocytopenia

Amniotic fluid embolism

Site of lodging, occlusion & characteristics	• uncommon and grave complication of labor and the immediate postpartum period, **caused by** infusion of amniotic fluid or fetal tissue into the maternal circulation via a tear in the placental membranes or rupture of uterine veins. • Microscopy: presence in the pulmonary microcirculation of squamous cells shed from fetal skin, fetal hair, fetal fat etc. Marked pulmonary edema and diffuse alveolar damage are also present. Systemic fibrin thrombi indicative of DIC can also be seen. • Characterized by sudden severe dyspnea, cyanosis, and hypotensive shock, followed by seizures and coma.
Complications	• Most (60-80%) are clinically silent because they are small. • when more than 60% of the pulmonary circulation is obstructed by emboli. Sudden death, infarction, right heart failure (cor pulmonale) occurs • If the patient survives the initial crisis, pulmonary edema develops, along with disseminated intravascular coagulation, owing to release of thrombogenic substances from amniotic.

Air embolism

Site of lodging & occlusion	Complications
-Gas bubbles within the circulation can obstruct vascular flow (& cause distal ischemic injury) acting as thrombotic masses. Bubbles may coalesce to form frothy masses sufficiently large to occlude major vessels. - Air may enter the circulation during **obstetric procedures** or as a consequence of chest wall injury (thoracic injury)	An excess of 100 cc is required to have a clinical effect. e.g.: • Decompression sickness

Decompression Sickness

A particular form of gas embolism

Causes

Occurs when individuals are exposed to sudden changes in atmospheric pressure.
→ When air is breathed at high pressure (e.g. during a deep sea dive), increased amounts of gas (particularly nitrogen) become dissolved in the blood and tissues. If the diver then ascends (depressurizes) too rapidly, the nitrogen expands in the tissues and bubbles out of solution in the blood to form gas emboli.

Risk

- High for Scuba and deep sea divers, underwater construction workers, and individuals in unpressurized aircraft in rapid ascent

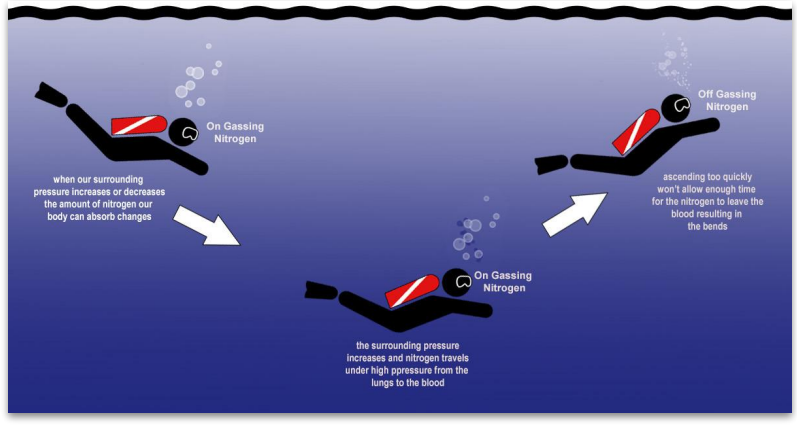
symptoms

- 'Grecian Bends' i.e. joint/muscle pain and 'chokes' i.e. respiratory distress.

treatment

Placing the individuals in a compression chamber where the **barometric pressure** may be raised, thus forcing the gas bubbles back into solution followed by subsequent slow decompression. so the person can breathe the nitrogen gas bubbles out

A more **chronic form** is called **caisson disease** in which, persistence of gas emboli in the skeletal system leads to multiple foci of ischemic necrosis; the more common sites are the heads of the femurs, tibia, and humeri.



Qulz

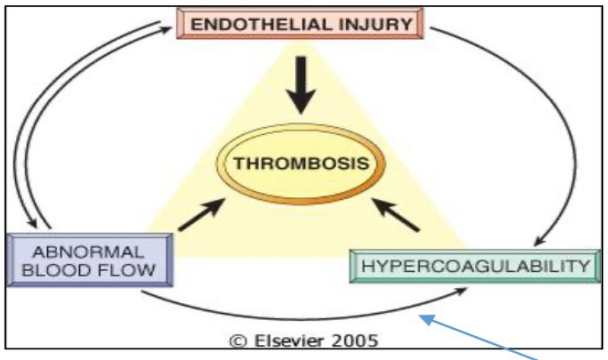
1- Harry is an 81-year-old man who presents to your A&E department with a 3-day history of breathlessness. He reports coughing up fresh blood and a sharp pain on the left side of his chest on taking a deep breath. what is the most likely diagnosis?			
a- pulmonary embolism	b- fat embolism	c- systemic embolism	d- air embolism
2- have capacity to embolize to the lungs and can cause death.			
a- arterial thrombi	b- hypertension	c- venous thrombi	d- hypotension
3- Hereditary Thrombophilia can be caused by deficiency of:			
a- protein C	b- protein A	c- protein S	d- both A and C
4-: A 55-year-old woman following major abdominal surgery has had discomfort and swelling of her left leg for the past week. On physical examination, the leg is slightly difficult to move, and on palpation there is tenderness. A Doppler sonogram shows thrombosis of deep left leg veins. Which of the following mechanisms is most likely to contribute to her condition?			
a- Turbulent blood flow	b- Immobilization	c- Atherosclerosis	d- Congestive heart failure
5-: A 22-year-old woman with an uncomplicated pregnancy develops sudden dyspnea with cyanosis and hypotension. She has a generalized seizure and becomes comatose. Her condition doesn't improve over the next 2 days. Which of the following findings is most likely to be present in her peripheral pulmonary arteries?			
a- Thromboemboli	b- Fat globules	c- Gas globules	d- Amniotic fluid
6- A 75-year-old man is hospitalized after falling and fracturing his left femoral trochanter. Two weeks later, the left leg is swollen, particularly below the knee. He experiences pain on movement of the leg; on palpation, there is swelling and tenderness. Which of the following complications is most likely to occur in this man?			
a- Disseminated intravascular coagulation	b- Fat embolism syndrome	c- Mural thrombosis	d- Pulmonary thromboembolism

1- a
2- c
3- d
4- b
5- d
6- b

Summary

This summary was taken from
The original slides

Objectives



1. Primary/Genetic
2. Secondary/acquired states

- Understand the basic pathogenesis of thrombogenesis and the risk factors for development of venous and arterial thrombosis.
- Know the types of emboli and to able describe the causes and pathology each one.

1. Pulmonary thromboembolism
2. Systemic thromboembolism
3. Fat embolism
4. Air embolism
5. Amniotic fluid embolism

Test your knowledge and try to match Column A with Column B

A
Intracardiac mural thrombi
Caisson disease
Saddle embolus
Fractures of long bones
Obstetric procedures
Decompression sickness
Grecian Bend
Deep vein thrombosis
Complication of labor and the immediate postpartum period
Deep sea divers
Presence of squamous cells, lanugo hair, fat, and mucin in pulmonary circulation

B
Pulmonary thromboembolism
Systemic thromboembolism
Fat embolism
Air embolism
Amniotic fluid embolism

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